



## **The Use of TRIPS Flexibilities for the Access to Hepatitis C Treatment**

**By Germán Velásquez**

**Special Adviser, Policy and Health, The South Centre**

### **I. General Context and Background on the Debate over Access to Medicines**

The problem of access to medicines until 2014 was concentrated in developing countries where one third of the world's population had no access to medicines, while industrial countries, thanks to public (Europe) and private (the United States of America) insurances managed to pay the cost of medicines. Currently the situation in developing countries remains the same but the great novelty, unprecedented, is that the industrialized countries are beginning to have difficulties in ensuring the supply of certain medicines to their citizens.

The debate and international negotiations on access to medicines began in 1995 with the creation of the World Trade Organization (WTO), at the end of the Uruguay Round, and the generalization of the mandatory use of patents for pharmacological products for all WTO member countries (currently totalling 164).

During the last 20 years, several important moments have marked the progress of the debate:

- 1995 Creation of WTO and with it the mandatory adoption of the TRIPS Agreement.

- 1996 World Health Assembly Resolution 49.14 on "Revised Medicine Strategy".
- 1997 "The WHO Red Book" on Globalization and access to medicines.
- 2001 (April) the South-African case in which 39 pharmaceutical companies lost a suit that sought to denounce the medicine law developed by the Mandela government. (June) The African Group of the WTO requests a debate on access to medicines. (November.) The DOHA declaration on Public Health and Intellectual Property.
- 2002 British Government Report on Intellectual Property and Development.
- 2006 World Health Organization (WHO) report on Intellectual Property and Public Health, known most widely by its English acronym CIPIH.
- 2008 Global Strategy on Medicines and Intellectual Property negotiated and approved by the WHO member States.
- 2012 "CEWG", a WHO report, recommends an international treaty on R&D.

### **Abstract**

In late 2013, a new Hepatitis C treatment called direct-acting antivirals (DAAs) was introduced in the market at unaffordable prices. The eradication of the disease is possible if medicines can be purchased at AFFORDABLE prices within health budgets. IF THIS IS NOT THE CASE, governments should consider the use of the TRIPS flexibilities to facilitate access to the treatment.

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*Fin 2013, un nouveau traitement contre l'hépatite C, appelé antiviraux à action directe (AAD), a été introduit sur le marché à des prix inabordables. L'éradication de la maladie est possible si les médicaments peuvent être achetés à prix ABORDABLES dans les limites des budgets nationaux de santé. SI CE N'EST PAS LE CAS, les gouvernements devraient envisager d'utiliser les flexibilités prévues dans l'Accord sur les ADPIC pour faciliter l'accès au traitement.*

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*A fines de 2013, se introdujo en el mercado un nuevo tratamiento para la hepatitis C, llamado antivirales de acción directa (AAD) a precios inasequibles. La erradicación de la enfermedad es posible si los medicamentos se pueden comprar a precios ACCESIBLES dentro de los presupuestos de salud. SI ESTE NO ES EL CASO, los gobiernos deberían considerar el uso de las flexibilidades de los ADPIC para facilitar el acceso al tratamiento.*

- 2013 (May) WHO demonstration projects: a distracting exercise?
- 2016 High-level Panel of the Secretary-General of the United Nations on Access to Medicines.

|       |            |
|-------|------------|
| 2013: | 6 products |
| 2014: | 5 products |
| 2015: | 3 products |
| 2016: | 1 products |

### I.1. Problems of the R&D Model

Let us recall that the current R&D model<sup>1</sup> for pharmaceutical products is based on the following scheme: **Research (private or public) - patent - monopoly - high price - restricted access**. This model contains several contradictions and problems that in the long run lead to a disarticulation between innovation and access. We will briefly refer here to three problems or faults of the current R&D model: 1) Lack of transparency of R&D costs. 2) Pharmacological innovation has effectively diminished in the last years. 3) High prices restricting access.

#### I.1.1. Lack of transparency of R&D costs

The cost, reported in 2014 by a study of Boston Tufts Center, for the development of a new molecule was of **2.5 Billion US\$**.<sup>2</sup> This is the figure currently used by the so-called originator pharmaceutical industry (i.e. “big Pharma”). However, in a study carried out by the London School of Economics in 2011,<sup>3</sup> the authors claim that the average cost to develop a new product is only 43.4 million US\$. The non-profit foundation DNDi (Drugs for Neglected Diseases initiative (DNDi) reported in 2013 that the average cost for research and development (R&D) of the **new chemical entities** that it had developed in its last 10 years of existence was between **100 and 150 million Euros**.<sup>4</sup>

As long as there is no clarity on the real cost of R&D, the problem of prices—and therefore of access to medicines—will continue to go unsolved. The massive difference between the estimates of 150 million US\$ or 2.5 Billion US\$ per molecule is significant, as the resulting price of the medicine would be significantly different.

#### I.1.2. Pharmaceutical innovation has significantly diminished in recent years

According to the data published by the French review *Prescrire* in recent years,<sup>5</sup> we find that the number of medicines that constant “an important therapeutic advance” introduced into the French market in the last 10 years are not more than 14 per year; furthermore, innovation appears to be diminishing, as the maximum number of 14 is significantly higher than the average number of yearly therapeutic advances over the past decade:

|       |             |
|-------|-------------|
| 2007: | 14 products |
| 2008: | 6 products  |
| 2009: | 3 products  |
| 2010: | 3 products  |
| 2011: | 3 products  |
| 2012: | 3 products  |

#### I.1.3. High prices restricting access

In 2014, the American firm Gilead Sciences introduced the hepatitis C drug Sofosbuvir (brand name Sovaldi) at the eye-watering price in the USA of 84,000 US\$, 57,000 Euros, for a 12-week treatment.

A recent study in the United States of America indicates that out of the 71 anti-cancer medicines registered between 2002 and 2014 by the FDA, many of them cost more than 100 US\$ per treatment.

Lack of transparency in the costs of R&D, a diminishing rate of pharmaceutical innovation in recent years and high prices all contribute to restrict access in both developing countries and developed ones. Collectively, these dynamics demonstrate a structural problem of the current R&D model for pharmaceutical products. Several documents discussed in the frame of WHO in the last 10 years, as well as a large number of studies and articles produced by scholars point to incoherence in the R&D model.

At the end of 2015, the Secretary General of the United Nations issued a call for a High-Level Panel on Access to Medicines; the panel would be constituted by an array of international experts of demonstrated competence. The terms of reference set for the expert group called for a study on “**The incoherence between the rights of inventors, international human rights legislation, trade rules and public health**”.

### I.2. What Has Changed in the Last Two Years?

The main new development is that the problem has now become global, involving both developing and developed countries. The totality of WHO documents and resolutions had previously referred to “diseases disproportionately affecting developing countries”. The distinction between communicable and non-communicable diseases, implied an understanding that only communicable diseases were affecting developing countries. However, nowadays, non-communicable diseases also represent a substantial source of morbidity and mortality for developing countries.

For the first time in history, there are medicines that industrialized countries cannot afford; this is demonstrated by, to cite just one example, their adoption of policies that effectively ration newer medicines against Hepatitis C and medicines against cancer.

The Human-Rights Commission of the United Nations tackles the issue from a human rights approach rather than a trade approach. In their 2015 deliberations, the Human-Rights Commission considered that access barriers to these medicines could be considered a human rights violation.<sup>7</sup>

### **I.3. A Paradigm Shift in the Debate on Access to Medicines: 2014-2018**

The pharmaceutical industry business model has changed. Previously, high R&D costs were being claimed (sometimes quite artificially) to establish high prices and increase profits. Nowadays the pharmaceutical industry, and this is precisely the case of Gilead, are, above all, financial industries whose first goal is to remunerate their shareholders and have managed to do what scholars and civil society organizations had been claiming for years, to de-link R&D costs from the final price of the product. However, the industry has attempted to co-opt this term by twisting the meaning. As Ruth Dreifuss expressed in the Graduate Institute of Geneva on the 23rd of February, 2017, the industry's twist on the concept suggests a "malefic de-linkage" through which cost and final price are unrelated and no attempt is made to reconcile the two.

## **II. The Hepatitis C Virus: Figures and Data<sup>8,9</sup>**

- Hepatitis C is a liver disease caused by the virus of the same name: the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness that can result in death.
- According to the World Health Organization (WHO), it is estimated that globally approximately 130 million to 150 million<sup>10</sup> people live with a chronic hepatitis C virus (HCV) infection and it is estimated that 700,000 people die each year from hepatitis C-related liver diseases.
- The hepatitis C virus is a blood-borne virus and the most common modes of infection are through unsafe injection practices, inadequate sterilization of medical equipment, and the transfusion of unscreened blood and blood products.
- HCV can also be transmitted sexually and can be passed from an infected mother to her baby; however these modes of transmission are much less common.
- Hepatitis C is not spread through breast milk, food, water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.
- New types of treatment and oral therapeutic regimens named Direct Action Antivirals (DAAs) may heal more than 90 per cent of Hepatitis C infection cases.
- Currently there is no vaccine for hepatitis C.
- The hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infection is usually asymptomatic, and is only very rarely

associated with life-threatening disease. About 15–45 per cent of infected persons spontaneously clear the virus within 6 months of infection without any treatment.

- The remaining 55–85 per cent of persons will develop chronic HCV infection, and in these cases the risk of cirrhosis of the liver is between 15–30 per cent within 20 years. According to WHO, an estimated 2.9 million of people living with HIV are infected with hepatitis C virus.<sup>11</sup>
- There are numerous HCV strains (or genotypes), variously distributed depending on the region.

## **III. Access to Hepatitis C Treatment**

### **III.1. The New Direct-Acting Antiviral Treatments**

Until the end of 2013, the standard treatment for Hepatitis C consisted of pegylated interferon injections over 24 to 48 weeks and complemented with ribavirin tablets twice a day. This treatment was costly, toxic, complicated to administer and with healing rates of less than 50 per cent.<sup>12</sup>

In late 2013, a new Hepatitis C treatment called direct-acting antivirals (or DAAs) was introduced in the market. In eight to twelve weeks of treatment these medicines could heal more than 90 per cent of persons with a chronic HCV infection.

The new DAAs treatments were introduced by the firms Gilead Sciences and Bristol Meyer Squib (BMS) in 2014. Gilead has patented or applied for patents for three DAA compounds: sofosbuvir, ledipasvir and velpatasvir.<sup>13</sup> BMS has patented or applied for a patent on daclatasvir.<sup>14</sup> As treatment in many cases must include both sofosbuvir and daclatasvir it means that there is a double barrier, two or more patents belonging to different firms. Other transnational firms such as AbbVie and Janssen have also put DAAs on the market, while additional products are in the "pipeline" of these and other firms.

### **III.2. Essential Medicines that Cure**

In April 2015, several DAAs were included in the WHO List of Essential Medicines. At the World Health Assembly in May 2016, WHO member countries approved the Global Health Strategy for Viral Hepatitis for the period 2016-2021.<sup>15</sup> This strategy aims to eliminate Hepatitis B and C as a public health menace by 2030. Elimination is defined as a 90 per cent reduction in incidence and a 65 per cent reduction in mortality. Achieving these goals implies extending treatment application to 80 per cent of the people living with chronic HBV and HCV diseases.

### **III.3. Sofosbuvir: Public Health or Financial operation.**

The American firm Gilead Sciences launched on the market—at a price of 84,000 US\$ for a 12-week treatment—the Hepatitis C medicine known as Sofosbuvir. A group of British academics<sup>16</sup> estimated that production costs for a twelve-week treatment could reach—in a figure that

includes a profit margin of 50 per cent – a price of 62 US\$. Nevertheless, Gilead Sciences has managed to negotiate prices with several governments that reveal large price differences between countries and, above all, prices that have nothing to do with production costs. 50,426 Euros in Germany, 41,680 Euros in France,<sup>17</sup> 13,000 Euros in Spain, 6,000 Euros in Brazil, 3,465 Euros in Australia.<sup>18</sup>

According to the quarterly sales reports of Gilead Sciences, historical sales of Sofosbuvir, commercially sold as “Sovaldi & Harvoni”, reached 40 billion US\$ by the first three quarters of 2016. Furthermore, Gilead’s 2015 profits reached 18 billion US\$, most of which may be attributed to the company’s Hepatitis C medicines. However, despite these massive profits, Gilead did not originally develop Sofosbuvir, as the product was developed by a small American company named “Pharmasset” that Gilead Sciences, realizing the potential of Sofosbuvir, acquired for 11 billion dollars in 2011.<sup>19</sup> This means that Gilead Sciences, in its first year of marketing sofosbuvir, fully recovered its investment. Such disproportionate returns –Gilead being but one example of many such cases– questions the justification of the 20 years of patent exclusivity provided by the WTO TRIPS Agreement.

It is worth remembering that Gilead was the company that sold “Tamiflu” for the H1N1 pandemic, giving exclusive exploitation to the Swiss company Roche. Many countries wasted large sums of money on precautionary procurement of a medicine that, in the end, scientists ultimately judged to be ineffective. Never in the history of modern medicine had “safety stocks” of such dimensions been made for a medicine whose efficacy was not proven.

### III.4. World Health Organization Standardized Treatment Guidelines

Recognizing the serious public health problem of HCV and the great promise represented by the new DAAs treatments, WHO developed in 2014<sup>20</sup> the first guidelines of standardized treatments. These guidelines were already reviewed in 2016 and 2017 due to the fast evolution of treatments for the different genotypes.<sup>21</sup>

### III.5. The Sofosbuvir Patents

It is important to keep in mind that when talking of patents for pharmaceutical products we are referring to patents of diverse types, as seen in the examples<sup>22</sup> below.

**Product patents:** claiming a chemical molecule/active pharmaceutical ingredient

**Process patents:** protecting the manufacture of a certain product. There are also many other types of patents, unaccepted by many countries as Argentina, Brazil or India, but among which we find hundreds and thousands of the current patents of pharmacological products, such as:

**Formulation patents:** of the dosage form, as, for example, on tablets of delayed release of the active ingredient.

**Combination patents:** claiming the combination of two or more existing active ingredients.

**Patents on salts, ethers and esters:** solid forms obtained by routine methods.

**Patents of polymorphic forms:** a polymorph is an intrinsic property of chemical products; polymorphs are not invented; instead they are only discovered and therefore should not be patented.

**Patents including a “Markush” claim:** very broad claims covering chemical structures that may include a family of thousands or millions of compounds.

**Selection patents:** claiming only a single element or segment of a Markush patent, for example, which was already included in the patented item.

**Patents on analogy processes:** covering an obvious method to produce a new compound.

**Patents on active metabolites and prodrugs:** metabolites are produced by the organism and cannot be considered an invented product. Prodrugs are inactive compounds that transform inside the organism into the therapeutically active ingredient, with which it shares the same active part of a molecule.

**Patents on treatment methods:** including prevention, diagnosis or prophylaxis methods; they do not protect a product itself but the way in which the product is used and, therefore, may not be patented since they lack a key patenting requirement: namely industrial application.

**Patents on second uses:** second uses or second indications of a product, over which there are already a great number of patents, should not be patentable as this is not a case of invention but of a discovery, which, in most cases, happens through medical practice and not in research laboratories of the pharmaceutical industries.

In the particular case of Sofosbuvir, a study conducted by WHO<sup>23</sup> revealed that this product is covered by 21 different types of patents: 2 Markush type patents that could give rise to dozens more, 4 process patents, 9 patents on salts and polymorphs, one patent on the combination of two products, and 3 patents on method of usage: “substance for the HCV treatment.”

Several of these Sofosbuvir patents are now the subject of litigation or oppositions in different countries, showing the fragility and lack of evidence that it should be considered a true genuine innovation. (Cf. 3.7.)

### III.7. Oppositions to the Sofosbuvir Patent of Gilead

The Non-Governmental Organizations I-MAK (Initiative for Medicines, Access & Knowledge) and the Delhi Network of Positive People (DNP+) presented an opposition to Gilead’s Sofosbuvir patent application in India. The lawyers of these two organizations claim that the

medicine represents “old science” and therefore does not meet the patentability standards of India.<sup>24</sup>

Sofosbuvir patents have been rejected in Egypt, China and Ukraine and have met oppositions in Argentina, Brazil, Russia, Thailand and the European Union.<sup>25</sup>

Two of the challenged cases in India make reference to the crystalline form of sofosbuvir and daclatasvir which in accordance to the Indian Patent Law, are not patentable unless evidencing a significant increase in therapeutic effect. There is a third opposition against velpatasvir (which combined with sofosbuvir is sold by Gilead under the brand name of “Epclusa”) because it is considered as an obvious modification of the structure of a previous medicine for Hepatitis C “ledipasvir” (which combined with sofosbuvir is sold by Gilead under the brand name of Harvoni).<sup>26, 27</sup>

### **III.8. Voluntary Licenses Granted by Gilead**

“In November 2013 and February 2014, public interest groups and generics companies filed the first patent oppositions against Gilead Sciences’ patent applications in India. Within months, Gilead signed voluntary license agreements with eleven Indian generics pharmaceutical companies and API manufacturers for the HCV DAAs sofosbuvir, ledipasvir and velpatasvir”.<sup>28</sup>

In 2014, Gilead issued voluntary licenses to 11 Indian manufacturers of medicine generics, giving them the possibility to market the product to a restricted list of 101 countries.<sup>29</sup> The prices of these Indian generic versions represent an important progress. (From September 2016 Sofosbuvir “under the Gilead license” costs 750 US dollars and the other two medicines, Harvoni and Epclusa, cost 900 US dollars per treatment<sup>30</sup>, instead of the 84,000 US dollars price in the United States.) However, its access is not allowed to the poorer countries of the restricted list.<sup>31</sup> In the other 94 countries excluded from the Gilead list, treatments are far from being accessible, and such rationing applies to many of the world’s richest countries, including ones from Europe and North America.

Negotiations for the introduction of voluntary licenses between the patent holder and another actor in a given country, or operating in that country’s market, may contribute to the reduction of prices. The benefits of voluntary licensing agreements depend largely on the conditions of the license itself.

Patent holders may, at their own discretion, issue to the other parties, exclusively or not, the rights to produce, import and/or distribute a pharmaceutical product. Depending on the terms of the license, the licensee may act completely or effectively as a representative of the patent holder, or be free to establish the conditions of sale and distribution of the product in a certain market or markets, in exchange for the payment of a royalty. Either of these options, or even intermediate agreements, can lead to a considerable reduction in prices. Nevertheless, the terms of a voluntary license may es-

tablish price margins or include clauses to keep prices at a similar price to that offered by the patent holder. Sometimes, export possibilities are limited, or anti-diversion measures are required, as is the case with Gilead and the 11 licenses granted to manufacturers in India. Again, such issues will depend on the conditions of the license agreement, and such contracts are often confidential.

Voluntary licensing agreements, usually at the discretion of the patent holder, take place in general for strategic commercial reasons (as for example to penetrate a market) rather than as a mechanism to ensure access to the largest number of people.<sup>32</sup>

MSF expressed worries concerning the voluntary licenses granted by Gilead in India, and these worries can be summarized as follows:<sup>33</sup>

- Gilead licensing obligations and restrictions can undermine access and exclude millions of patients with HCV.
- There are approximately 49 million people living with HCV in developing countries who have been excluded by this license.
- Gilead’s license for DAAs lacks transparency and can be translated as an “evergreening” strategy.
- Gilead has provided no information on the type of applications being submitted in the excluded countries. Gilead has applied for secondary patents (crystallization forms, compositions, etc.) that, although weak and easy to reject in principle, will block competition from generic medicines in the countries where they are accepted.
- The definition of patents in voluntary licenses is too broad, (includes patents and patent applications), and refers to both primary and secondary patents as treatment method patents. This fact leads to a certain ambiguity, as for instance whether it would be possible to export or not to a country excluded from the Gilead licenses but issuing a compulsory license.
- Gilead has negotiated its voluntary licenses both for the end product and for the raw material (APIs) only with India but not with China or Brazil for example, and this is problematic in terms of the expansion of a global market of generics.
- Gilead has segmented the APIs market by means of the following strategies: firms licensed by Gilead may only obtain APIs through other licensees from India or from other Gilead suppliers, with its prior approval.
- Gilead does not authorize its licensees to import from potential Chinese manufacturers who would be able to produce much cheaper APIs and other intermediate substances.

All countries excluded from the voluntary license of Gilead (or other companies arriving to similar agree-

ments) do have legal options on which to lean to ensure supply of DAAs or any other essential medicine protected by a patent at inaccessible prices. This section enumerates the different strategies and measures that countries can adopt to ensure universal access to the DAAs treatments:

#### IV. How to Overcome the Barriers to Access Using TRIPS Flexibilities

The voluntary license granted by Gilead to 11 generic manufacturers of India excludes, besides all developed countries, 41 middle-income countries.

##### IV.1. Information on International Prices

Care must be taken during negotiation with the originating companies regarding the conditions eventually included in the contracts, such as renouncing to use some flexibilities of the TRIPS Agreement, or waiving parallel imports, or admitting import restrictions of raw material.

patents, just as the production process for the product can also be protected by one or numerous patents; therefore, in many countries there exist several types of patents that are applied to a single pharmaceutical product. (According to the previously mentioned WHO study,<sup>36</sup> Sofosbuvir is the subject of 21 types of patents. As a result, a single medicine can be protected by a large number of patents.

The patentability requirements used by national intellectual property offices, according to the TRIPS Agreement, require a product or manufacturing process to meet the conditions necessary to grant patent protection, namely: novelty, inventive step and industrial applicability (utility). These three elements, however, are not defined in the TRIPS Agreement and WTO Member States are free to define these three criteria in a manner consistent with the public health objectives defined by each country.

Middle-income countries excluded from the voluntary license of Gilead<sup>34</sup>

|                        |                    |            |                    |
|------------------------|--------------------|------------|--------------------|
| Albania                | Costa Rica         | Kosovo     | Saint Lucia        |
| Argentina              | Dominican Republic | Lebanon    | Syria              |
| Armenia                | Ecuador            | Macedonia  | Thailand           |
| Azerbaijan             | Georgia            | Malaysia   | Turkey             |
| Belarus                | Grenada            | Mexico     | Ukraine            |
| Belize                 | Hungary            | Moldova    | Venezuela          |
| Bosnia and Herzegovina | Iran               | Montenegro | West Bank and Gaza |
| Brazil                 | Iraq               | Panama     | Yemen              |
| Bulgaria               | Jamaica            | Peru       |                    |
| China                  | Jordan             | Romania    |                    |
| Colombia               | Kazakhstan         | Serbia     |                    |

It is also advisable to know the prices of generics in the countries where the DAAs have not being patented, in order to evaluate whether it is needed or not to issue a compulsory license to ensure universal access.

##### IV.2. Adoption of Patentability Criteria from a Public Health Perspective<sup>35</sup>

It is important to remember that a patent is a territorial right and that it is therefore possible that a patent is granted for an invention in one country but that the very same patent application could be legally rejected by another country. In the same manner, a patent that has been issued in one country can be revoked if it is demonstrated that the patent office should not to have granted it.

It is also important to highlight that in the pharmaceutical sphere, the situation is not ONE product, ONE patent. An invention can be protected by numerous

According to the report of the United Nations High Commissioner for Human Rights “the requirements under the TRIPS Agreement for the grant of patents – novelty, inventive step and industrial applicability – are open to interpretation under national legislation and each country can decide according to local conditions. Consequently, the High Commissioner encourages interpretations of these requirements that do not lose sight of the public interest in the wide dissemination of knowledge...”<sup>37</sup>

The fact that the TRIPS Agreement does not define novelty, inventive step and industrial applicability (utility) leaves countries significant room for manoeuvre; therefore **patentability requirements represent the principal and most important flexibility allowed by the Agreement to protect public health and access to medicines.** “Politicians and legislators have broad room for manoeuvre to give legal effect to those flexibilities”.<sup>38</sup>

### IV.3. Compulsory Licenses – Aspects and Practical Procedures<sup>39</sup>

Article 31 of the WTO TRIPS Agreement explicitly allows the granting of compulsory licenses. The Agreement contains no limits on the grounds under which such licenses can be granted. Members' right to determine such grounds has been confirmed by the Doha Declaration on the TRIPS Agreement and Public Health (November 2001).

Article 31 makes particular, but not exhaustive, reference to cases of national emergency or extreme urgency, dependency of patents, licenses for governmental non-commercial use, and licenses to remedy anti-competitive practices. National laws can, however, provide for the granting of such licenses whenever the titleholder refuses to grant a voluntary license "on reasonable commercial terms" (Article 31 (b)) and for other reasons, such as public health or broad considerations of public interest. The Agreement permits that compulsory licenses provide licensees the authority to exercise any of the rights conferred by a patent, including production or importation.

The granting of a compulsory license within the framework of national legislation (and in conformity with the TRIPS Agreement) requires a body of measures described below.

#### IV.3.1. Identify relevant patents

It is often a true challenge for ministries of health to identify all primary and secondary patents around a given product. Historically, patent offices and health ministries have not developed strong links between them; however, countries such as Argentina, Brazil, Thailand, Ecuador or India have started to establish such links in order to make effective use of the flexibilities of the TRIPS Agreement, notably the granting of compulsory licenses. In 2015, WHO published – with the promise to keep it updated – a study of the landscape of the patents related to Hepatitis C, a very useful tool for countries wishing to issue a compulsory license or to make parallel imports. There is also a database, developed by MPP, with the landscape of HCV patents.<sup>40</sup>

In most cases, pharmaceutical products are protected by a patent for the active ingredient (primary patent) and by different (secondary) patents for formulations, production processes, new indications, etc. All these patents must be identified and included in the compulsory license, as appropriate, in order to be able to ensure the autonomy to develop the necessary product. Otherwise, the use of the invention targeted by the compulsory license may be disturbed or blocked by allegations of infringement of the secondary patents (as exemplified by the well documented case of the DDI product in Thailand).

#### IV.3.2. Explore possible sources of supply based on local production

The analysis to be undertaken should include:

- the availability of technical resources for reverse engineering;
- the cost and duration of developing manufacturing processes and formulations;
- the need for technology transfer;
- GMP and quality of final products made by local producers; and
- estimates of the investment required and of the marginal cost of production.

#### IV.3.3. Identify possible sources of importation of the required medicines

The analysis to be undertaken should include:

- compliance with GMP and product quality assurance by potential suppliers;
- prices of supply over time; and
- the sustainability of the exporter's supply.

#### IV.3.4. Marketing approval

Registration requirements may represent an obstacle to rapid distribution of the necessary medicines, as could happen, for example, when the country has introduced a period of exclusivity for the protection of data coming from tests. When examining the possibility of issuing a compulsory license, all necessary measures should be taken to ensure that these obstacles will not be present or may be overcome.

#### IV.3.5. Request for a compulsory license

The applicable conditions will depend on the alternatives and modalities chosen by each country according to its national legislation. A request to the patent holder on reasonable commercial terms should be made, including:

- information about the requesting party;
- the expected volume of production;
- the royalty to be paid;
- the form of payment;
- the intended mode of use of the invention;
- quality controls;
- trademark to be used, if any;
- the duration of the license;
- the licensee's right to control sales for determination of royalties due;
- the applicable law and jurisdiction in case of disputes.

Some laws and regulations do not delimit a "reasonable period of time" for the patentee to accept or reject the offer, but a period of one to three months may be considered reasonable.

When dealing with governmental use, no prior negotiations are required; "public interest" constitutes a legitimate reason to grant a compulsory license.

Declaring a "national emergency" is not a requirement for a compulsory license to be granted. When choosing this option, it should be borne in mind that an "emergency" can be a long-term situation, as it happens with the HIV/AIDS pandemic, and not just a short-term problem.

In many cases a compulsory license for government use is preferable both because no prior negotiations are required and also because it will be clear from the start that the government's basic criterion for granting a compulsory license is public health. In this way, it is politically more difficult for patent holders, their trade associations and their respective governments to question the compulsory license.

#### ***IV.3.6. Granting of the compulsory license by the competent department***

The competent department will have to define the scope of the license and its duration. It would be advisable for the scope to include all commercial and non-commercial uses of the relevant invention, and for the license to last until the patent's expiry.

#### ***IV.3.7. Negotiation with patent holder about royalty rate***

After the granting of the compulsory license, bona fide negotiations should be undertaken with the patent holder to establish the royalty rate for the exploitation of the patent. Generally, these royalties are determined as a percentage of the net sales price of the generic product made under the license (and not the patentee's own product), but other modalities can be adopted, for instance, a fixed sum per unit sold.

The TRIPS Agreement requires that the compensation reflect the economic value of the license. Commercial practice in voluntary licensing is to use royalties ranging between 2 per cent and 5 per cent, though they may be higher in certain cases. There is some evidence available on the royalties determined by national authorities in Canada, the USA, and other countries for the granting of compulsory licenses.<sup>41</sup>

Factors that may be considered to negotiate the royalties include: launch date of the product; possible substitutes; coverage and possible invalidity (total or partial) of the patent(s); pending challenges to the patent(s), if any; accumulated sales and recovery of R&D investment made by the patent holder; global market for the product (units and value); expected volume of production and price under the compulsory license; and royalties agreed upon in voluntary licenses

on the same or similar products. Gathering this information will require considerable preparation and work by an inter-disciplinary team.

#### ***IV.3.8. Determination of royalty fee by the Patent Administration Department***

If the negotiations on the royalty fee fail, it will be set by the Patent Administration Department or the corresponding body charged with the relevant authority by law. For the sake of transparency and consistency, it would be advisable to make explicit the criteria used for this purpose and to design guidelines applicable to all such determinations of royalty fees.

#### ***IV.3.9. Appeal***

National legislations establish the modalities by which patent holders may file an appeal against a decision to grant a compulsory license; it is important that the appeal does not suspend the execution of the aforementioned compulsory license.

#### ***IV.3.10. Other considerations***

Patent holders (or their governments) may attempt to use legal measures, such as injunctions, to delay or prevent the execution of a compulsory license. It would also be useful to check for the possible application of other instruments, such as bilateral agreements on investment (or BITs), which often consider intellectual property as an "asset" subject to their rules.

## **Conclusions**

- The eradication of the disease is only possible if medicines can be purchased at low prices within health budgets.
- New ways of delivering mass treatment programmes for Hepatitis C are needed.
- It is necessary to become conscious of the problem, raise awareness, diagnose and, in many cases, refer the patient to another level of care, evaluate the stage of the disease, follow the treatment and monitor the patient's progress.
- Most medicines have low production costs; pharmaceutical companies could make high levels of profit if they would decide to sell large quantities at reasonable prices.

If pharmaceutical companies refuse to lower prices, it would be necessary to consider:

- Compulsory licenses.
- Parallel imports.
- Promotion of the manufacture of generics.
- Summoning them before Justice for a violation of Human Rights.

Endnotes:

<sup>1</sup> Model that must obligatorily follow all members of the World Trade Organization nowadays.

<sup>2</sup> Tufts Center for the Study of Drug Development, “Cost of developing a new drug” Boston, November 2014.

<sup>3</sup> Donald W. Light and Rebecca Warburton “Demythologizing the high costs of pharmaceutical research”, [http://www.pharmamyths.net/files/Biosocieties\\_2011\\_Myths\\_of\\_High\\_Drug\\_Research\\_Costs.pdf](http://www.pharmamyths.net/files/Biosocieties_2011_Myths_of_High_Drug_Research_Costs.pdf).

<sup>4</sup> DNDi, “Research & Development for Diseases of the Poor: A 10-Year Analysis of Impact of the DNDi Model”, Geneva 2013.

<sup>5</sup> Rev. *Prescrire*, “L’année 2016 du médicament: un système qui favorise l’imitation plutôt que la recherche de réels progrès.” Paris, Page 136 Tome 37 No. 400.

<sup>6</sup> Ariadna Tibau, MD1; Alberto Ocana, MD, PhD2; Geòrgia Anguera, MD1; et al, “Oncologic Drugs Advisory Committee Recommendations and Approval of Cancer Drugs by the US Food and Drug Administration”. *JAMA Oncology* 2016;2(6):744-750. Available from: <http://jamanetwork.com/journals/jamaoncology/article-abstract/2497879>.

<sup>7</sup> HRC Resolution on “Access to medicines in the context of the right of every one to the enjoyment of the highest attainable standard of physical and mental health”, Geneva, 2016.

<sup>8</sup> WHO Facts sheet: <http://www.who.int/mediacentre/factsheets/fs164/en/>.

<sup>9</sup> Ref. International Association of providers of Aids Care: [http://www.aidsinfonet.org/fact\\_sheets/view/674](http://www.aidsinfonet.org/fact_sheets/view/674).

<sup>10</sup> This data has been revised by WHO and the estimation is now 70 million.

<sup>11</sup> WHO, Global Health Sector strategy on viral Hepatitis 2016-2021: Towards ending viral hepatitis. <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>, p. 11.

<sup>12</sup> Manns MP, Wedemeyer H, Cornberg M. “Treating viral hepatitis C: efficacy, side effects, and complications”. *Gut* 2006;55(9):1350-9.

<sup>13</sup> Gilead Sciences, 2016 <http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-irhome>.

<sup>14</sup> MSF briefing, [https://www.msfastcess.org/sites/default/files/MSF\\_assets/HepC/Docs/HepC\\_brief\\_OvercomingbarriersToAccess\\_ENG\\_2015.pdf](https://www.msfastcess.org/sites/default/files/MSF_assets/HepC/Docs/HepC_brief_OvercomingbarriersToAccess_ENG_2015.pdf).

<sup>15</sup> WHO/HIV/2016.06.

<sup>16</sup> Gotham D, Barber M, Fortunak J, Pozniak A, Hill A. Abstract number A-792-0516-01639, presented at AIDS2016, Durban.

<sup>17</sup> On 17th. March, 2017 the French government announced a new reduction to 28,700 Euro for a 12-week treatment; a price which still remains larger than double of what Spain pays. “Soins : le prix des médicaments contre l’hépatite C va baisser”. [http://www.leparisien.fr/laparisienne/sante/soins-le-](http://www.leparisien.fr/laparisienne/sante/soins-le-prix-des-medicaments-contre-l-hepatite-c-va-baisser-31-03-2017-6812619.php)

[prix-des-medicaments-contre-l-hepatite-c-va-baisser-31-03-2017-6812619.php](http://www.leparisien.fr/laparisienne/sante/soins-le-prix-des-medicaments-contre-l-hepatite-c-va-baisser-31-03-2017-6812619.php).

<sup>18</sup> Price for a 12-week treatment.

<sup>19</sup> FOSTER CITY, Calif. & PRINCETON, N.J., “Gilead Sciences to Acquire Pharmasset, Inc. for \$11 Billion”, <http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle&ID=1632335>.

<sup>20</sup> WHO, Guidelines for the screening, care and treatment of persons with hepatitis C infection. <http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/>.

<sup>21</sup> WHO, “Global report on access to hepatitis C treatment. Focus on overcoming barriers, Geneva, October 2016, p. 22.

<sup>22</sup> Carlos Correa, “Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective”. WHO, ICTSD, PNUD, UNCTAD, Geneva, 2008.

<sup>23</sup> WHO, Patent situation of key products for treatment of hepatitis C: Sofosbuvir, Geneva, March 2015.

<sup>24</sup> MSF “Access: Patent challenge hearing on Gilead hepatitis C drug sofosbuvir starts in India”, <http://www.msf.org/en/article/access-patent-challenge-hearing-gilead-hepatitis-c-drug-sofosbuvir-starts-india>.

<sup>25</sup> Ibid.

<sup>26</sup> MSF, “Flawed patents on hepatitis C drugs latest to be challenged in global push for access” February 2017. <https://msfastcess.org/about-us/media-room/press-releases/flawed-patents-hepatitis-c-drugs-latest-be-challenged-global-push>.

<sup>27</sup> A copy of the patent oppositions can be found with the following links:

<https://www.patentoppositions.org/en/drugs/daclatasvir>

<https://www.patentoppositions.org/en/drugs/sofosbuvir>

<https://www.patentoppositions.org/en/drugs/velpatasvir>

<sup>28</sup> MSF Access Campaign, “Access to Sofosbuvir, Ledipasvir and Velpatasvir analysis & key recommendations on Gilead voluntary licence, March 2015.

<sup>29</sup> MSF Briefing Document, [https://www.msfastcess.org/sites/default/files/MSF\\_assets/HepC/Docs/HepC\\_brief\\_OvercomingbarriersToAccess\\_ENG\\_2015.pdf](https://www.msfastcess.org/sites/default/files/MSF_assets/HepC/Docs/HepC_brief_OvercomingbarriersToAccess_ENG_2015.pdf).

<sup>30</sup> <http://www.gilead.com/~media/files/pdfs/other/chronic%20hepatitis%20c%20medicines%20pricing%20-%20september%202016.pdf>.

<sup>31</sup> Access to the generics made under Indian voluntary licenses is restricted only to the poorer countries that comprise the license territory.

<sup>32</sup> Velasquez, G., Correa C., Weisman R. “Cost-containment mechanisms for essential medicines, including antiretrovirals, in China” Health Economics and Drugs EDM Series No. 13, WHO/EDM/PAR/2003.6.

<sup>33</sup> Ibid.

<sup>34</sup> MSF briefing, version of November, 2016: [https://www.msfastcess.org/sites/default/files/MSF\\_assets/HepC/Docs/HepC\\_brief\\_OvercomingbarriersToAccess\\_ENG\\_2015.pdf](https://www.msfastcess.org/sites/default/files/MSF_assets/HepC/Docs/HepC_brief_OvercomingbarriersToAccess_ENG_2015.pdf).

[pC/Docs/HepC\\_statement\\_AnalysisOfGileadLicense\\_ENG\\_2015.pdf](#).

<sup>35</sup> Velasquez, G. "Guidelines on Patentability and Access to Medicines", *Research Paper* 61, South Centre, March, 2015.

<sup>36</sup> WHO, Patent situation of key products for treatment of hepatitis C: Sofosbuvir, Geneva, March 2015.

<sup>37</sup> The impact of the Agreement on Trade-Related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, paragraph 62.

<sup>38</sup> Arias, Eduardo, PPT on "Pautas para el examen de patentabilidad de invenciones químico-farmacéuticas, INPI, Argentina, 2014.

<sup>39</sup> This point on the aspects and practical procedures for the granting of a Compulsory License is based on the article by Velasquez G., Correa C., Weisman R. "Cost-containment mechanisms for essential medicines, including antiretrovirals, in China", Health Economics and Drugs EDM Series No. 13, WHO/EDM/PAR/2003.6.

<sup>40</sup> See <http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/>.

<sup>41</sup> Niess, P. "Technology evaluation and pricing". *Tech Monitor*, November-December 1999, pp. 16-17.



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Chemin du Champ d'Anier 17  
PO Box 228, 1211 Geneva 19  
Switzerland  
Telephone: (4122) 791 8050  
Fax: (4122) 798 8531  
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